REMARKS

Status of the claims

Claims 20-33 are pending in the application. Claims 20-33 stand rejected in the application. Claims 1-19 and 34-59 are withdrawn. No new matter is added.

The 35 USC §103 rejection

Claims 20-33 stand rejected under 35 USC §103(a), as being unpatentable over **Larsen** *et al.* (U.S. Patent No. 6,592,843) in view of **Scheinberg** *et al.* (U.S. Patent No. 6,683,162) and **Wartchow** *et al.* (US2003/0082103 A1). The Applicant respectfully traverses the rejection.

The Examiner states that **Larsen** *et al.* disclose the encapsulation of radionuclides that emit alpha particles, such as Pb-212, Ac-225 into a typical size of 100nm liposome to generate a radionuclide-liposome conjugator system with PEG-affinic groups to reduce interference from plasma proteins, and thus reduce clearance by macrophages in the spleen and liver (reticuloendothelial system). The Examiner also states the radionuclide is incorporated into the liposome as a chelation compound of radionuclide and-EDTA, DPTA, *etc.*, and that **Larsen** *et al.* teach administration of the liposomes to humans to target tumors. **Larsen** *et al.* do not disclose entrapment of a radionuclide inside a small liposome, which is incorporated into a large liposome. Finally, the Examiner states

that **Larsen** *et al.* do not disclose use of large liposomes having a diameter of 600 to 1000 nm, nor use of HERCEPTIN® antibody labeling on the surface of large liposome.

The Examiner states that **Scheinberg** *et al.* disclose an Ac-225 complex attached to an antibody or fragment thereof, such as HERCEPTIN® and administered to treat cancer cells. The Ac-225-antibody conjugate may be administered to humans to treat breast cancer.

The Examiner states that **Wartchow** *et al.* disclose radiotherapeutic liposomal constructs comprising a radionuclide-chelator conjugaton compound, targeting entity (antibody) and stabilizing entity (PEG). The radiotherapeutic liposomal constructs are used to target cancerous tissue with radionuclides while leaving healthy tissue unaffected. The liposomes of the disclosure may be bilayer structures that encapsulate a therapeutic agent and may be the size of 1000nm. These multilamellar vesicles are rapidly taken up into the reticuloendothelial system, *i.e.* liver and spleen, which causes them to remain in the circulatory system for hours. The targeting agents may be HERCEPTIN®, biotin, etc.

The Applicant submits that **Larsen** *et al.* teach a conjugator system comprising liposomes with ionophores and with chelator and heavy radionuclide inside liposomes, wherein liposomes are stably labeled with heavy radionuclides emitting alpha particles. Also, **Larsen** *et al.* teach a method of preparing the

radionuclide-containing liposomes by active incorporation of the radionuclide via ionophores within the liposome and prepared according to procedures yielding liposomes of typical size equal to 100nm. The liposomal membranes may be PEGylated and/or attached to monoclonal antibodies (col. 2, ll. 57-62).

The Applicant submits that **Scheinberg** *et al.* disclose use of chelated Ac-225 covalently attached to an antibody, antibody fragment, growth factor, or cytokine and administered in a pharmaceutically acceptable carrier to humans to treat cancer.

The Applicant submits **Wartchow** *et al.* disclose a lipid construct comprising a linking carrier, a targeting entity, and optionally, a therapeutic entity ([0054]).

The Applicant submits that the claimed invention is directed to a method of targeting cells in an individual for liposomal delivery of an alpha particle-emitting radionuclide with reduced systemic release of radioactive decay intermediates to reduce non-specific cytotoxicity. The instant invention uses chelated alpha particle-emitting radionuclides passively entrapped into small liposomes, which are encapsulated in the aqueous phase of large liposomes of a sufficient diameter to retain a majority of the radioactive decay intermediates, and these large liposomes are labeled with agents that allow for cell-specific targeting thereby reducing systemic release of radionuclides. The combination of a small

radiolabeled liposome encapsulated within a large liposome creates a multivesicular liposome, with different properties and characteristics from unilamellar or multilamellar liposomes.

Based on the cited prior art of **Larsen** *et al.* (U.S. Patent No. 6,592,843) in view of **Scheinberg** *et al.* (U.S. Patent No. 6,683,162) and **Wartchow** *et al.* (US2003/0082103 A1), the Examiner concludes it would have been obvious to one of ordinary skill in the art to prepare radiotherapeutic liposomal constructs of sizes 100-1000nm where optimization of size depends on the desired application, for instance taken up by the reticuloendothelial system (pg 5, 2nd PP). Further, the Examiner concludes that since **Wartchow** *et al.* disclose that the radiotherapeutic liposomal construct may be encapsulated within a multilamellar liposome then one would have a reasonable expectation of successfully attaching a targeting agent, such as HERCEPTIN® or biotin to the liposome for site specific (pg 5, 2nd PP). The Applicant respectfully disagrees.

The Applicant submits that **Larsen** *et al.* do not teach or disclose radiolabeled small liposomes contained within a large liposome of sufficient size to retain a majority of radioactive decay intermediates, which together produce a multivesicular liposome. Further, Applicant submits that **Larsen** *et al.* do not teach or disclose passive entrapment of chelated Ac-225 into small liposomes but rather specify an ionophore is required to actively transport the radionuclide across the lipid bilayer. Finally, **Larsen** *et al.* do not teach or disclose antibodies such as

HERCEPTIN® to allow targeting specificity of radiolabeled multivesicular liposomes to tumor cells.

These deficiencies of **Larsen** *et al.* are not remedied by **Scheinberg** *et al.* **Scheinberg** *et al.* do not disclose use of Ac-225 entrapment in liposomes nor disclose retention of radioactive decay intermediates in multivesicular liposomes. The instant specification teaches that non-specific distribution of radionuclides is toxic and occurs when the bond between the targeting vehicle, *i.e.*, antibody or fragment thereof, is broken by the transformation of the parent through emission of first alpha particle, which leaves the first daughter in the decay chain free to distribute throughout the body and increase non-specific tissue toxicity (instant invention, pg 5, lines 16-20). Thus the instant invention uses target-labeled multivesicular liposomes to contain the radioactive particles and their decay intermediates thereby allowing specificity of the cytotoxic effects.

The deficiencies of **Larsen** *et al.* and **Scheinberg** *et al.* are not remedied by **Wartchow** *et al.* **Wartchow** *et al.* do not disclose use of 1000nm liposomes but rather disclose production of very large multilamellar vesicles of 1000-10,000 nm as a step in the process of making the correctly sized unilamellar liposomal vesicles of 50-100nm for maximum *in vivo* circulation time ([0078]). Further, **Wartchow** *et al.* disclose large multilamellar vesicles are rapidly removed from circulation by the reticuloendothelial system (liver and spleen) thus the **Wartchow** *et al.* invention typically utilize unilamellar vesicles having an average

diameter of less than 200nm, preferably less than 100nm, and even more preferably 60-80 nm so that they will remain in circulation for hours ([0079]).

To anticipate the invention, a prior art reference must fairly teach all the claim elements so that one of ordinary skill in the art is motivated to make the modification with a reasonable expectation of success. One of ordinary skill in the art would not be motivated to increase the size of the liposomes in the conjugator system of **Larsen** *et al.*, because **Larsen** *et al.* teach an effective radionuclide-containing liposome of 100 nm diameter has prolonged circulation time *in vivo*. Further, motivation is lacking in **Larsen** *et al.* to produce multivesicular liposomes since only unilamellar liposomes are specified. No motivation for modification to the instant invention can be found in **Scheinberg** *et al.* since this invention does not disclose use of liposomal encapsulation of alpha-emitting radionuclide particles. As well, **Wartchow** *et al.* provide no motivation to modify to use large multivesicular liposomes, because **Wartchow** *et al.* teach large liposomes are removed by the reticuloendothelial system. Thus, **Wartchow** *et al.* prefer to use 50-100nm size unilamellar vesicles to optimize *in vivo* circulation time.

Taken together, **Larsen** *et al.*, **Scheinberg** *et al.*, and **Wartchow** *et al.,* provide no motivation to use large multivesicular liposomes to contain the radionuclide parent and daughter particles. The Examiner has presented no scientific basis or legal argument for the conclusion based on the prior art of **Larsen** *et al.* with **Scheinberg** *et al.* and **Wartchow** *et al.* Therefore, the subject

matter of the instant claims are not rendered obvious. Accordingly, in view of the arguments presented herein, Applicants respectfully request that the rejection of claims 20-33 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action, mailed August 29, 2007. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution. Applicant encloses a Petition for a Three Month Extension of Time. Please charge the $525 fee to the credit card identified on the enclosed Form PTO-2038. Only in the absence of Form PTO-2038, please debit any applicable fees from Deposit Account No. 07-1185 upon which the undersigned is allowed to draw.

Respectfully submitted,

Date: Feb 27, 2008

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
Tel: (713) 270-5391
Fax: (713) 270-5361
BEN@adlerandassociates.com